REMARKS

Claims 40, 42, 44, 46, 56-58, and 61 are presently pending. The Applicants respectfully thank the Examiner for withdrawing all the obviousness rejections that were on record in the last Office Action. Nevertheless, the Examiner has now asserted a new reference (i.e., Meade et al.) in combination with previously asserted secondary references. The Applicants object to this improper piecemeal examination strategy. *MPEP 707.07(g)*. In other words. where has Meade et al. been all these years, and why is the Examiner only now asserting the reference if it was not considered relevant in the past ?

The new obviousness rejections are rebutted in the following order:

I. Rejections Under 35 USC §103(a)

A. Claims 40 and 61 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), Seegers et al. Blood 5:421-433 (1950), and further in view of van Cott and Velander *Expert Opinion on Investigational Drugs* 7:1683-1690 (1998).

B. Claims 40, 42, 44, 46, 56 and 58 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

C. Claims 40 and 57 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al. in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Seegers et al., *Blood* 5:421-433 (1950); and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

I. The Claims Are Not *Prim Facie* Obvious

The Examiner is reminded that *KSR v Teleflex* has not changed basic law regarding obviousness determinations. The USPTO Guidelines admit as such, and provide for the situations wherein obviousness may be found. The Applicants do not believe that the Examiner has meet the burden of these guidelines.

Further, the *KSR* holding only cautioned against a strict application of the "teaching-suggestion-motivation test" such that an explicit teaching is not required to be found within the cited applications. Nevertheless, it is still required to: i) establish *some motivation* to combine

the references either explicitly or implicitly, and ii) establish a *prima facie* case of obviousness, wherein the prior art reference (or references when combined) must teach or suggest all the claim limitations. The Applicants submit that the Examiner has not made a *prima facie* case of obviousness.

A. Meade et al. And Jorgensen et al. Do Not Teach A Fully Carboxylated Recombinant Prothrombin Polypeptide

The Applicants' note that the Examiner has provided three separate obviousness rejections. Notably, all the obviousness rejections depend upon an improper combination of Meade et al. and Jorgensen et al. The Applicants provide below rebuttal evidence showing that this improper combination of Meade et al. and Jorgensen et al. do not teach all the claimed elements, thereby rebutting the Examiner's alleged *prima facie* case of obviousnes.

The Examiner states that Meade et al. is:

> ... an efficient means of producing large quantities of recombinant protein in the milk of transgenically altered mammals. A DNA sequence coding for a desired protein is operatively linked in an expression system to a milk-specific protein promoter or any promoter sequence specifically activiated in mammary tissue ...

Office Action pg 4, that when placed in combination with Jorgensen et al. make the Applicants' claimed invention allegedly obvious. The Applicants disagree.

The Examiner is reminded that *KSR* left untouched the requirement that a *prima faice* case of obviousness must provide evidence that all the claimed elements are disclosed in the asserted references. Such a showing of evidence is required under the *KSR* holding as the Court reinforced the need for a proper *Graham* analysis to support any obviousness rejection. In one aspect of a proper *Graham* analysis, the Examiner must identify and consider the differences between the cited art and the Applicants' claimed invention. In this case, the differences are significant, as the combination of references do not teach a recombinant prothrombin polypeptide comprising a fully carboxylated Gla domain (i.e., this is a missing element which immediately obviates a *prima facie* case of obviousness). *KSR* requires an Examiner to provide an explicit analysis to support the obviousness rejection:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents ... To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some

> articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

KSR v Teleflex, 127 S. Ct. 1727, 1740 (2007) [emphasis added]. This, the Examiner has not done. 'Articulated reasoning" requires a plausible discussion that, at a minimum, compares and contrasts the teachings of an asserted reference with the Applicants' specification. Merely pointing to single words, without the appropriate context, is wholly insufficient. As shown above, *KSR* cites *In re Kahn* to explain this requirement:

> ... mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. [*In re Rouffet*, 149 F.3d] *at 1355, 1357.* ... to establish a prima facie case of obviousness ... the Board must articulate the basis ... In practice ... [t]his entails consideration of ... the "scope and content of the prior art" ...

In re Kahn 441 F.3d at 986 [emphasis added]. The Examiner has lined up several references (i.e., for example, Jorgensen et al., Seegers et al., van Cott et al., and Le Bonniec et al.) which are pointed to for various isolated elements that is limited to the 'mere identification in the prior art of each element'. However, as more fully explained below, the Examiner still has not found all the Applicants' claimed elements.

Here, the Examiner admits that Meade et al. does not teach all the claimed elements:

> ... Meade et al. ... do[es] not indicate that recombinant prothrombin is made in milk.

Office Action pg. 4. The Applicants further submit that not only does Meade et al. not teach recombinant prothrombin in milk, Meade et al. also does not teach a recombinant prothrombin comprising a fully carboxylated Gla domain in milk. To provide a *prima facie* case of obviousness the Examiner must now provide a reference that supplies this missing element. The Examiner has not met this burden. Instead, the Examiner offers Jorgensen et al. which is limited to an *in vitro* experiment performed in Chinese Hamster Ovary cells:

> Jorgensen et al. teach that expression vector comprising the coding sequence of human prothrombin was used to express in Chinese Hamster Ovary (CHO) cells ...

Office Action pg 5. The Examiner has clearly not properly considered the scope and content of Jorgensen et al. because the reference has no context related to making and using transgenic

animals using high protein expression platforms. This is the very issue that *In re Kahn* held against. Additionally, in contrast to the Examiner's assertion, Jorgensen et al. provides context that teaches away from the Applicants' claimed embodiment:

> When prothrombin expression levels are amplified 10-15 fold, however, only approximately 60% of the secreted prothrombin is sufficiently carboxylated to bind to the conformation-specific antibodies. ... It appears that the γ-carboxylation system has a limited capacity for the amount of substrate which can be efficiently processed over a given period of time; when the rate of substrate synthesis exceeds this limit, the extent of γ-carboxylation is reduced.

Jorgensen et al., pg 6733, lhc. As such, Jorgensen et al. does not provide any reasonable expectation of success that the disclosed plasmids are useful to produce fully carboxylated prothrombin at high expression levels.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claim 40 to recite that the recombinant prothrombin has a milk concentration of "at least 0.5 mg/ml". The Examiner may find exemplary support for this amendment as follows:

> The results from assays of transgenic pig milk shows prothrombin in the milk at levels between 0.5 and 5.0 mg/ml.

Applicants' Specification pg 49 ln 2-3, and

> The early lactation milk from this mouse contained 5.5 ± 2.1 mg/ml of prothrombin, based on the quantitative Western analysis.

Applicants' Specification pg 53 ln 25-26. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application. As shown above, Jorgensen et al. clearly states that the expressed prothrombin polypeptides are not fully carboxylated at expression levels of this magnitude.

Consequently, the combination of Meade et al. nor Jorgensen et al. do not teach the claimed element of a recombinant prothrombin protein comprising a fully carboxylated Gla domain. Therefore, the Examiner's combination of Meade et al. and Jorgensen et al. fails to create a *prima facie* case of obviousness in regards to all of the Applicants' pending claims. The Examiner is respectfully requested to withdraw all the pending rejections.

B. Seegers et al. Is Of No Help

The Examiner states that in regards to Claim 40 and 57:

> Seegers et al. teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate ...

Office Action pg 7. The Examiner has not shown that Seegers et al. remedies the deficiencies of Meade et al. and Jorgensen et al. by teaching a highly expressed fully carboxylated recombinant prothrombin. Consequently, the Applicants argue that Claim 40 is patentable, thereby mooting the rejections under Seeger et al. to dependent claims.

C. van Cott et al. Is Of No Help

The Examiner states that in regards to Claims 40 and 61:

> According to van Cott and Velander, while transgenic mice were poor at gamma-carboxylating recombinant proteins, transgenic pigs were able to gamma-carboxylate recombinant proteins excreted tin milk up to 0.1 g/l/h ..

Office Action pg 6. The Applicants submit that the Examiner has ignored the fact that van Cott et al. were <u>not</u> discussing the γ-carboxylation of prothrombin:

> ... the mouse mammary gland was a very poor γ-carboxylator of recombinant <u>Protein C and FIX</u>, while the pig was able to γ-carboxylate up to 0.1 g/l/h ...

van Cott et al., pg 1686 rhc – 1687 lhc [emphasis added]. First, the Applicant's claimed embodiment recites prothrombin, not Protein C and Factor IX. Second, van Cott et al. does not provide evidence that Protein C and Factor IX were fully carboxylated, only that γ-carboxylation in pigs is better than in mice. Third, the prothrombin expression level now recited in Claim 40 is 5 times superior to that referred to in van Cott et al. (i.e., 0.1 g/l/h = 0.1 mg/ml/h).

The Applicants submit that van Cott et al. does not provide sufficient teachings, such that when combined with Meade et al. and Jorgensen et al., that one having ordinary skill in the art could make and use a transgenic mammal capable of secreting transgenic prothrombin iin milk at a level of at least 0.5 mg/ml.

D. Le Bonniec et al. Is Of No Help

The Examiner states that:

> Le Bonniec et al. teach that prothrombin is activated by bovine factor Xa ... [and] that activiation of prothrombin yields thrombin ...

Office Action pg 6. The Applicants argue that Le Bonniec et al. does not remedy the lack of a prima facie case of obviousness in view of the other asserted references discussed above. Specifically, Le Bonniec et al. does not provide any evidence teaching recombinant prothrombin in the milk of a transgenic mammal having a concentration of at least 0.5 mg/ml.

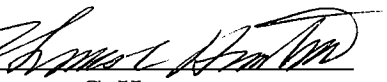
E. Conclusion

The Examiner has not provided any evidence showing that milk produced by a transgenic mammal can have at least 0.5 mg/ml of fully carboxylated recombinant prothrombin. As such, the Examiner has failed to put forth a *prima facie* case of obviousness. The Examiner is respectfully requested to withdraw all the pending rejections and pass the above claims to allowance.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

Dated: October 20, 2008

By: 

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